child's illness to the familiar idiopathic diarrhoea of toddlers ('irritable bowel syndrome') is also under investigation. In such cases of unexplained diarrhoea, a therapeutic trial of aspirin may be justified.

The drug loperamide, which was also effective in our patient, antagonizes prostaglandin-induced diarrhoea in adults, and has been shown to block the smooth muscle stimulating action of prostaglandins, acetylcholine, and histamine on gastrointestinal smooth muscle preparations from several laboratory animals (Karim and Adaikan, 1977).

Summary

A child with chronic diarrhoea since birth responded to the prostaglandin synthetase inhibitors aspirin and indomethacin. During a period without treatment, raised levels of prostaglandins $F_2\alpha$ and E_2 were observed. No source for these raised prostaglandins was shown, and it is suggested that she may have an inborn defect of prostaglandin metabolism.

We thank Dr. S. C. Sharma for the gift of antisera to $PGF_2\alpha$ and PGE_2 .

References

- Allan, J. D., Mason, A., and Moss, A. D. (1973). Nutritional supplementation in treatment of cystic fibrosis of the pancreas. *American Journal of Diseases of Children*, **126**, 22-26.
- Karim, S. M. M., and Adaikan, P. G. (1977). The effect of loperamide on prostaglandin-induced diarrhoea in rat and man. *Prostaglandins*, **13**, 321-331.
- Lloyd-Still, J. D., and Demers, L. (1976). Prostaglandin E and enterocolitis. (Abst.) *Pediatric Research*, **10**, 357.
- Lundstrom, V., Wiqvist, N., and Green, K. (1977). Prostaglandins and dysmenorrhea. *International Conference on Prostaglandins*, Florence, May 1975, Abstr. p. 222 (in press).
- Pickles, V. R., Hall, W. J., Best, F. A., and Smith, G. N. (1965). Prostaglandins in endometrium and menstrual fluid from normal and dysmenorrhoeic subjects. *Journal of Obstetrics and Gynaecology of the British Commonwealth*, **72**, 185-192.
- Rees, W. D. W., and Rhodes, J. (1976). Altered bowel habit and menstruation. (Letter.) *Lancet*, **2**, 475.
- Sharma, S. C. (1972). A sensitive radioimmunoassay for prostaglandins F. *Journal of Physiology*, **226**, 74p-75p.

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Association of fatal Coxsackie B₂ viral infection and necrotizing enterocolitis

The aetiology of necrotizing enterocolitis (NEC) is uncertain, despite much interest and research. The clinical course, pathology, and various proposed aetiologies of NEC have been extensively discussed (Stevenson *et al.*, 1969, 1971; Virnig and Reynolds, 1974). From these reviews it seems likely that many factors play a role in the development of this disease. Although viruses have been implicated in a wide variety of other gastrointestinal diseases (Howard and Simmons, 1973), there has been little evidence that viral infection may be a causal factor in NEC. We present a case of an association between a disseminated viral infection and NEC to emphasize the possibility that viral agents may be part of the spectrum of causes of NEC.

Case report

A 3-day-old white male, weighing 2760 g, was admitted to the University of Colorado Medical Center because of suspected sepsis. Both parents suffered from a febrile illness at the time of his birth. Prominent physical findings on admission were marked abdominal distension and tenderness, bilious vomiting, bloody diarrhoea, and fever. Pneumatosis intestinalis was noted on abdominal x-rays. The diagnosis of NEC was made and treatment was begun with oral and parenteral antibiotics, correction of fluid and electrolyte imbalance, and other supportive measures.

He rapidly deteriorated clinically. Exploratory laparotomy showed marked abdominal wall and retroperitoneal oedema, a moderate amount of straw-coloured ascitic fluid, and filmy adhesions about the stomach, liver, spleen, and transverse colon. Most of the ileum appeared ischaemic and cyanotic with multiple areas of subserosal haemorrhage, but there was no frankly necrotic intestine, and no bowel was resected. Therapy was resumed, including gavage-fed and intravenous antibiotics. His condition worsened and he died 30 hours later. His course before death was marked by a falling haematocrit, hypotension, cardiomegaly, and rapidly-developing bilateral pulmonary infiltrates.

Gross findings at necropsy examination showed severe bilateral haemorrhagic pneumonia, a small atrial septal defect (secundum), oedema and haemorrhage of the terminal ileum, and moderate retroperitoneal oedema. Histological examination showed pulmonary haemorrhage, areas of mucosal and subserosal intestinal haemorrhage, and evidence

of hepatic congestion with periportal oedema and venular and lymphatic dilatation. Microscopical evidence of retroperitoneal haemorrhage was present. There was no evidence of frank intestinal perforation or infarction. Bacteriological and virological data are summarized in the Table.

Discussion

The first description of neonatal NEC has been attributed to Genersich (Stevenson *et al.*, 1971). Since then the pathophysiology and clinical course have been increasingly well defined. Several causes have been suggested (Virnig and Reynolds, 1974), including bacterial infection, Schwartzman reaction, mesenteric ischaemia due to the 'diving reflex', hypoxia, and complications of umbilical artery catheterization such as infection, embolism, or intestinal blood flow redistribution.

Various types of enterovirus are known to cause gastrointestinal disease. A few investigators have suggested a role for viral infection in the development of NEC. Izant (1973) mentioned an association of enterovirus and NEC. Kibrick and Benirschke (1958) reported fatal viral sepsis with Coxsackie B₄, but the gastrointestinal manifestations in their patients were minor. Lake *et al.* (1976) reviewed enteroviral infections at our institution and found three positive enteroviral cultures among 28 neonates with NEC. Virnig and Reynolds (1974), in a limited epidemiological study of patients with NEC, were unable to document a viral aetiology.

Our patient died from viral infection. This in itself is rare and represents the extreme end of a spectrum of illnesses resulting from enteroviral

infection. It is also unusual in that there was no histological evidence of significant hepatic or cardiac involvement and less histological evidence of ischaemia and necrosis of the small bowel than might have been expected. It is uncertain whether NEC developed because of Coxsackie B₂ infection in our patient. Though the viral infection and NEC may well have been causally related, the association may have been a coincidence, or both could have been manifestations of a third factor such as immunological deficiency. Since it is still uncertain what causes NEC, further investigation of this possible aetiological factor seems warranted. Only by careful viral cultures and serological studies can the importance of viral agents in NEC be assessed.

Summary

A case of fatal Coxsackie B₂ viral infection and coexisting neonatal necrotizing enterocolitis occurred. We suggest that this virus may have a role in the development of NEC.

References

- Howard, R. J., and Simmons, R. L. (1973). Viral infections and the surgical patient. *Surgery, Gynecology and Obstetrics*, **137**, 1029–1046.
- Izant, R. J., Jr., (1973). (Discussion): Kosloske, A. M., and Martin, L. W. Surgical complications of neonatal necrotizing enterocolitis. *Archives of Surgery*, **107**, 223–228.
- Kibrick, S., and Benirschke, K. (1958). Severe generalized disease (encephalohepatomyocarditis) occurring in the newborn period and due to infection with Coxsackie virus Group B. Evidence of intrauterine infection with this agent. *Pediatrics*, **22**, 857–875.
- Lake, A. M., Lauer, B. A., Clark, J. C., Wesenberg, R. L., and McIntosh, K. (1976). Enterovirus infections in neonates. *Journal of Pediatrics*, **89**, 787–791.

Table Viral and bacterial culture data

Specimen	Pre-mortem cultures		Post-mortem cultures	
	Viral	Bacterial	Viral	Bacterial
Patient				
Nasopharynx	Coxsackie B ₂	Staphylococcus epidermidis (rare) Micrococcus (rare) Streptococcus viridans (rare)	Coxsackie B ₂	—
Throat	Coxsackie B ₂	No β-haemolytic streptococcus	Coxsackie B ₂	—
Rectal swab	Coxsackie B ₂	No enteric pathogens	—	—
Cerebrospinal fluid	—	No growth	—	No growth
Blood	Coxsackie B ₂	No growth	Coxsackie B ₂	No growth
Urine	Coxsackie B ₂	No growth	Coxsackie B ₂	—
Peritoneal fluid	—	No growth	—	No growth
Umbilical swab	—	—	—	No growth
Lung	—	—	Coxsackie B ₂	No growth
Spleen	—	—	Coxsackie B ₂	No growth
Liver	—	—	Coxsackie B ₂	No growth
Mesenteric nodes	—	—	Coxsackie B ₂	—
Mother				
Rectal swab	Coxsackie B ₂	—		
Throat	No growth	—		
Nasopharynx	No growth	—		
Urine	No growth	—		

- Stevenson, J. K., Graham, C. B., Oliver, T. K., and Goldenberg, V. E. (1969). Neonatal necrotizing enterocolitis. *American Journal of Surgery*, **118**, 260-272.
- Stevenson, J. K., Oliver, T. K., Graham, C. B., Bell, R. S., and Gould, V. E. (1971). Aggressive treatment of neonatal necrotizing enterocolitis: 38 patients with 25 survivors. *Journal of Pediatric Surgery*, **6**, 28-35.
- Virnig, N. L., and Reynolds, J. W. (1974). Epidemiological aspects of neonatal necrotizing enterocolitis. *American Journal of Diseases of Children*, **128**, 186-190.

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Significance of vesicoureteric reflux

Sir,

I was a little disturbed at the unsubstantiated conclusion made by Moncrieff and Whitelaw (*Archives*, 1976, **51**, 893) that vesicoureteric reflux (VUR) in the absence of a complicating urinary tract infection (UTI) does not cause renal damage. Although the majority of patients with VUR come to clinical attention because of a UTI, there is now compelling evidence from radiological studies in infants and children (Rolleston *et al.*, 1975), renal function studies in children (Aperia *et al.*, 1976), and morphological studies in pigs (Hodson *et al.*, 1975) that progressive renal damage may occur in the context of gross VUR. This damage may develop and progress in the continued absence of complicating UTIs. In addition, early surgery to correct gross VUR may lead to a resumption of normal renal growth despite the fact that successful antireflux surgery does not influence the incidence of subsequent UTIs (McRae *et al.*, 1974).

Moreover if intrarenal reflux can be shown, focal renal scarring may develop in the areas of affected renal parenchyma (Rolleston *et al.*, 1974; Uldall *et al.*, 1976; Bourne *et al.*, 1976). The significance of intrarenal reflux has been confirmed in studies of the pathogenesis of reflux nephropathy in the pig experimental model (Hodson *et al.*, 1975). Infection was not an essential factor in scar formation but it did intensify the scarring process. The main conclusion from these human and animal studies is that gross VUR, and not UTI, is essential for the development of renal damage. The observation that the severity of the VUR is the single most important determining factor as to whether renal damage will occur has been the major breakthrough in the understanding of this subject in recent years (Bailey, 1973).

The recent letter in your journal by Cowen (*Archives*, 1977, **52**, 254) should be regarded with caution. Cowen concluded that a micturating cystourethrogram was not worthwhile in the investigation of an infant with a UTI if the intravenous urogram was normal. This statement was based on a study of only 20 neonates and cannot be supported in the light of a substantial number of published reports (including, in this journal, Drew and Acton, 1976) which have shown that 50-60% of infants under

the age of one year with a UTI have VUR, and more importantly that in 8-13% of these the VUR is gross in degree. In the latter patients the intravenous urogram may appear normal. I agree, however, that a micturating cystourethrogram is not indicated if a good quality intravenous urogram has been shown to be completely normal in a child over the age of 4 years.

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Dr. M. Moncrieff comments:

We thank Dr. Bailey for drawing our attention to this point. In the discussion of our results we quoted Smellie and Normand (1975) who state that new renal scars 'almost invariably develop' in association with infection. We should have repeated this phrase in the summary. However, the point of our paper was that with a normal intravenous urogram (IVU) 'gross VUR' which 'is essential for the development of renal damage' is very unlikely to be present, being found in only 2 of 70 ureters in our series. Cystography is undoubtedly unpleasant and sometimes hazardous (McAlister *et al.*, 1974), and we feel that our suggestion of deferring cystography until a second infection occurs in those with a normal IVU is the lesser of two evils.

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References

- Aperia, A., Broberger, O., Ericsson, N. O., and Wikstad, I. (1976). Effect of vesicoureteral reflux on renal function in children with recurrent urinary tract infection. *Kidney International*, **9**, 418-423.
- Bailey, R. R. (1973). The relationship of vesico-ureteric reflux to urinary tract infection and chronic pyelonephritis—reflux nephropathy. *Clinical Nephrology*, **1**, 132-141.
- Bourne, H. H., Condon, V. R., Hoyt, T. S., and Nixon, G. W. (1976). Intrarenal reflux and renal damage. *Journal of Urology*, **115**, 304-306.